by doctors skilled in the art. When the guidance and direction provided by Applicant's specification disclosure, the level of knowledge and the content of the prior at the time of the invention as established in the record, the high level of skill in the art, and Applicant's declaration evidence are interpreted in a reasonable manner, analysis considering the factors in In re Wands compels a conclusion that undue experimentation would not be required to practice the invention called for in the appealed claims.

Once the relevant materials and administration techniques set forth in Applicant's specification and those known in the art when the application was filed, are properly considered in their entirety, Applicant believes that there should be no question that one skilled in the medical art is enabled to make and use the claimed invention. This conclusion is reinforced by the fact that the materials and administration techniques, but not the inventive result, were well known when the instant application was filed.

For the above reasons, Applicant submits that the rejection of claims 403, 411, and 412 for lack of enablement under 35 U.S.C. §112, second paragraph, is contrary to current law, and perforce, should be withdrawn.

Rejection of Claims 404 and 405
under 35 U.S.C. §112, First Paragraph Enablement

Applicant hereby repeats and relies upon the above presented remarks regarding the rejection of claims 403, 411, and 412 and submits the following remarks in support of the enablement of claims 404 and 405.

Claims 404 and 405 depend from claim 403 and call for intramuscularly injecting stem cells into a patent's leg (claim 404) or heart (claim 405). The specification, page 21, broadly describes administering soft tissue promoting compositions using a hypodermic needle. The

specification, at page 45, discloses intramuscularly injecting such compositions into the leg or heart to promote the growth of an artery. Examples 18 and 19 describe specific protocols for intramuscular injection into the leg (Example 18) and the heart (Example 19). Pages 47 and 48 of the specification describe reimplanting a patient's own cells, i.e., stem cells to promote direct differentiation and morphogenesis into an organ, such as an artery.

Those workers versed in the medical art are well aware of the techniques employed for isolating mononuclear stem cells from bone marrow and peripheral blood. The practice of intramuscular injection of therapeutic agents is so common and well known in the medical art that the PTO should take Official Notice of this fact in evaluating the of scope of enablement provided by the specification.

Rejection of Claims 407-410
under 35 U.S.C. §112, First Paragraph – Enablement

Applicant hereby repeats and relies upon the above presented remarks regarding the rejection of claims 403, 411, and 412 and submits the following remarks in support of the enablement of claims 407-410.

Claims 407-410 depend directly or indirectly from claim 403 and call for stem cells harvested from bone marrow or blood. The specification, at page 45, discloses intramuscularly injecting such compositions into the leg or heart to promote the growth of an artery. As noted earlier, the specification describes using adult (autologous) stem cells harvested from the bone marrow or peripherial blood of the patient. See pages 40-42, 47, and 48 of the specification in this regard. Pages 47 and 48 of the specification describe reimplanting a patient's own cells, i.e., stem cells to promote direct differentiation and morphogenesis into an organ, such as an artery.

Stem cells and the practice of handling, storing, culturing and implantation of stem cells, including those of the patient, harvested bone marrow and blood are so common and well known in the medical art that the PTO should take Official Notice of these facts in evaluating the scope of enablement provided by the specification.

For the above reasons, Applicant submits that the rejection for lack of enablement under 35 U.S.C. §112, second paragraph, of claims 403-405 and 407-412 is contrary to current law, and perforce, should be withdrawn.

The following remarks pertain to new issues raised by the PTO in the Office Action

At page 13, ¶12 of the Office Action, the PTO confirms its position that all claims must be considered as a group, rather than individually, in the evaluation of enablement. This is patent nonsense. When evaluating enablement, it is incumbent upon the PTO to determine what subject matter each claim recites, i.e., the scope of protection sought for each claim. The scope of dependent claims are properly determined with respect to 35 U.S.C. §112, fourth paragraph. See MPEP Section 2164.08. It is clear that the present PTO's Examiner's analysis did not treat the subject matter of each claim separately or treat the dependent claims according to statutory mandate. Applicant believes that it is incumbent upon the present PTO Examiner to follow established law and PTO procedures.

At page 13, ¶19-22 of the Office Action, the PTO merely repeats the three points identified and discussed by Applicant regarding an evaluation of enablement and reiterates the PTO's ultimate conclusion. In such repetition the PTO correctly acknowledges that :

> Thus Applicant agrees that the state of the art at the time the instant application was filed did not include any support or disclosure of the growth of new arteries by administering stem cells.

While the above acknowledgement may explain the absence of a prior art rejection, such acknowledgement is not relevant to the issue of enablement of the disclaimed and claimed invention. What the PTO appears not to understand is that, while individual elements of the claimed invention were known in the art at the time the instant application was filed, the concept of combining of such elements and the resultant artery formation were not known or achieved in the art. Hence, once the concept is known to a skilled medical person, the actual combination of elements and result are no more than a matter of routine medical practice.

At pages 15-32, ¶23-47 of the Office Action, the PTO presents a series of gratuitous and disparaging remarks regarding the specification. Rather than roaming throughout the specification and then making such remarks, the PTO should read the portions of the specification that deal with the claimed invention. The PTO should keep in mind that the specification discloses numerous inventions, such as those identified in the several restriction requirements of record in the instant application. Obviously, the PTO should focus upon the portions of the disclosure related to the elected cell invention. The declarations of Drs. Heuser and Lorincz identify and then focus upon such relevant portions to evaluate enablement regarding the claimed invention. The PTO is urged to read the disclosures referenced in connection with the respective enablement opinions and then focus upon these identified, relevant portions.

In any event, such gratuitous and disparaging remarks contain serious technical errors and misunderstandings and thereby lack credibility. Some of the more serious errors are presented below.

One of the more serious errors in the PTO's position, at page 17 of the Office Action, is that those skilled in the art at the time the application was filed understood that stem cells

harvested from bone marrow and blood referred to the CD34+ fraction. There is no evidence of record supporting the PTO's position. CD34+ stem cells are a sub-fraction as evidenced by Isner. The newly submitted Fourth Supplemental Declaration of Dr. Richard Heuser (attached hereto as Exhibit A) and the Third Supplemental Declaration of Dr. Andrew E. Lorincz (attached hereto as Exhibit B), originally filed February 24, 2010, in co-pending application Serial No. 10/179,589 confirm Applicant's position. The Declarants attest that to a contrary understanding of those skilled in the medical arts, i.e. that the expression "stem cells harvested from bone marrow" is understood to refer to the entire population. Hence, the PTO's lack of understanding with the content of the knowledge of the art at the time the application was filed is demonstrated. An adjunct to this serious technical error is the PTO's highly erroneous assertion at page 19 of the Office Action is that CD34+ endothelial progenitor stem cells can produce artery growth. The above-mentioned declarations demonstrate error in this aspect as well.

In connection with the present PTO Examiner's erroneous analysis that CD34+ cells alone function to form arteries, at page 19 of the Office Action, the present PTO Examiner makes the nonsensical statement that Applicant could take a contrary position and argue such position. Applicant has not urged any such result and, in fact, the present PTO Examiner's position is not factually sound. This spurious "issue" is a prime example as to why the present record has become so lengthy.

At page 28, ¶40 of the Office Action, the PTO characterized the term "cascade of genetic material" as a malapropism. In this regard, Applicant notes the following statement of Dr. William O'Neil found in The Journal of Invasive Cardiology, Vol. 17, July 1, 2005, article entitled "Tissue Engineering and Interventional Cardiology" (of record). A complete copy of the

above article was made of record by Applicant because the copy furnished by the present PTO Examiner (of record) was incomplete and did not contain the following quotation:

> … in terms of the degree of our ignorance about the basic science in this area. My own feelings is that God – or nature – in His infinite wisdom, is a lot smarter than we will be for a few centuries yet in terms of the cascade of the processes that actually allow a new cell to come in and regenerate.

Such quotation is evidence that those skilled in the medical art reading the specification would fully understand which cells are intended and the methodology for implanting such cells as well as the terminology used by Dr. Elia in describing the necessary *in vivo* cascade of processes that allow implanted cells to regenerate in a patient's body. Prior to deeming the term to be a malapropism, the present PTO Examiner deemed such term to be nonsense. Apparently Dr. O'Neil was able to educate the present PTO Examiner to the extent that the term is no longer nonsense. Moreover, there are other versions of this well known medical terminology in the record of this an co-pending applications of Dr. Elia that are not exactly the same as used by Drs. O'Neil and Elia. Perhaps the present PTO Examiner can educate Applicant as to which of these versions are malapropisms and explain why this is the case. Such non-relevant "issue" is simply another reason as to why the instant record has grown to such length.

At pages 29 and 30, ¶¶41 and 42 of the Office Action, the PTO again questions *how* to use stem cells to grow an artery. The simple answer provided by the specification is to place such cells into the body of a human patient by, for example via injection. The body then completes the process, as disclosed in the specification, by growing an artery via direct differentiation and morphogenesis along genetically predetermined pathways. Such process is remarkably simple from a medical standpoint once the inventive concept is disclosed. In this regard, the PTO's citation of a page 45, lines 1-4 is noted. Of course, because genes are

mentioned, one skilled in the art would recognize that cells could be likewise employed to grow an artery.

At page 30, ¶44-47 of the Office Action, the PTO erroneously states that the stated goal of the claimed method includes "growing a new artery." Such identified "goal" does not appear in the claims, and thus the present PTO Examiner is in error. Being that such premise is in error, the comments in ¶¶45-47 are likewise not relevant to the claims under examination.

At pages 32-37, ¶¶48-55 of the Office Action, the PTO continues to critique a conversion technique that has been in existence in the medical field for a long period of time. In rebuttal, the PTO is referred to Applicant's above remarks involving this issue, as well as those presented below.

If the present PTO Examiner wishes to improve such well known and employed conversion technique, Applicant is sure that the medical field would welcome any improvement. However, the use of such calculation to demonstrate dosage conversions has between demonstrated twice by Applicant and confirmed to be reasonable by medical experts Drs. Heuser and Lorincz. Such evidence should put an end to this issue, especially since the present PTO Examiner has not introduced any evidence and thus appears to have engaged in puffery.

In any event, the PTO's *ad hominem* criticism of Applicant's conversion set forth at fails to adequately give weight to its evidentiary value. Applicant's evidence establishes as a material fact that physicians have long used conversion charts/formulas for estimating dosages of cells from nucleic acids and vice versa. It is clear from the record that cell survival and differentiation are not paramount considerations in determining cell dosages because the general practice is to employ multiple doses since stem cell overdosing has not proved to be problematic. Most importantly, there is no guidance proffered by Isner regarding the need to employ disparate

treatments for the delivery of cells *vis-à-vis* genes. Those skilled in the art are aware that safe dose ranges have been established over years of medical practice directed to bone marrow transplant cell therapy. The PTO's attention is again directed to the expert opinions of Drs. Heuser and Lorincz (of record), which validate the reasonableness of Applicant's dosage conversions. These two experts in the medical art have confirmed the reasonableness of using such art recognized conversion and Applicant has already provided two instances of the conversion in regard to Strauer and Isner. In view of such evidence and the lack of any evidence from the present PTO Examiner, it becomes the burden of the present PTO Examiner to provide material evidence, not unsupported opinion and hubris, that the conversion is not appropriate.

The present PTO Examiner has previously taken the position that even if Applicant "…stumbled upon some simple method for determining cell numbers to use in therapy…" that this would not evince enablement because the specification fails to teach such a conversion misses the point. There is neither need nor requirement for the instant specification to disclose the challenged conversion. Applicant has not professed to be the originator of the commonly employed calculus used to determine cell numbers to use in therapy. The simple answer is that the specification does not have to describe information already known by those skilled in the medical arts. See In re Buchner, supra. That the present PTO Examiner lacks knowledge of this routine conversion commonly used by skilled medical practitioners is not dispositive of this issue. The PTO has failed to establish why one skilled in the art of cell therapy would not be able to extrapolate the referenced examples in the instant specification across the entire scope of the claims. See MPEP Section 2164.02.

At pages 38 and 39, ¶¶56 and 57 of the Office Action the PTO takes issue with Applicant's explanation in the specification that the mechanism for artery growth involves

differentiation and morphogenesis. The mechanism of artery growth is not contained in the claims and it is trite law that an applicant is not required to identify, or be correct if identification is made, the mechanism by which an invention operates. It is sufficient, as noted earlier, that Applicant describes multiple mechanisms in the specification for growing soft tissue, such as arteries, which are organs.

The PTO cited the Ziegelhoeffer et al. publication to allegedly show that artery growth does not occur through direct differentiation and morphogenesis in a murine model. The PTO's attention is directed to pages 1656 and 1657 of Strauer 2005 that multiple mechanisms (multifactorial) are involved with the regenerative potential of bone marrow – derived stem cells and include direct differentiation as well as the stimulation of endogenous stem cells, etc. which are responsible for cell-biologic and molecular mechanisms resulting in organ growth for human beings. This is consistent with Applicant's disclosure. It is Applicant's position that one skilled in the art would understand that Strauer's work on humans necessarily trumps Ziegelhoeffer's work on a murine model. Strauer 2005 specifically points out that the precise mechanism for artery growth is undeterminable. In any event, it is axiomatic that an inventor is not required to explain the exact theory of the invention.

At pages 40-42, ¶¶58-62 of the Office Action, the PTO again relies upon Strauer as evidence that the more than routine experimentation would be required to practice the claimed invention. Applicant disagrees.

In the Office Action, the PTO apparently takes the position that the mere designing of the Strauer trial regarding cell population, administration technique, and transplantation timing somehow constitutes evidence of undue experimentation. However, when challenged previously, the PTO could not point to any experimentation actually performed by Strauer, for

good reason. This latest position by the PTO regarding Strauer constitutes a further change of the explanation regarding the evidentiary value of this publication. The PTO apparently has relied upon Strauer as establishing that a determination of cell population is critical, citing pages 1916-1917 of the publication. The PTO fails to point to any specific teaching in the record, which supports this proposition, and for good reason. Careful review of this publication fails to reveal any teaching that experimentation was required to determine cell population.

Applicant again calls the PTO's attention to Nabel as evidence that methods and apparatus employed by Strauer were well known. Nabel confirms the fact that no experimentation was required by Strauer because old, well known methods and apparatus, such as the off the shelf angioplasty technique of Nabel, were used. Applicant cites Nabel to show that experimentation as to administration technique was not required by Strauer. The fact that Nabel failed to use the type of cells necessary for achieving the claimed result, i.e., growing arteries, does not detract from the fact that such administration was known in the medical art prior to Applicant's 1998 filing date. Hence, no experimentation was required by Strauer regarding the delivery technique.

The concept of containment to prevent back flow and prolong contact time is clearly taught by Nabel. Thus, contrary to the PTO's prior assertion, it is clear that Strauer did not require or perform any experimentation to choose an appropriate delivery system or devise a containment system that would prevent backflow of cells and thus provide a prolonged time for cell implantation. Rather, such choice constitutes no more than the routine use of a well-established delivery system. Additionally, it is noted that Nabel does not support a notion that experimentation was required in regard to cell dosages.

The present PTO Examiner previously asserted in co-pending applications that, "…considerable experimentation was done, if not by Strauer, then by others in order to determine the effective cell population" without citing any instances of experimentation. Such statement serves as an admission that Strauer performed no experimentation, and thus directly contradicts the statements regarding Strauer in the Office Action. Applicant teaches that the entire array of bone marrow mononuclear cell components contribute to the regeneration of ischemic tissue, and such teaching is consistent with Orlic, Strauer, and Dohmann, which confirm that mononuclear bone marrow cell components promote artery growth. In the absence of evidence provided by the PTO showing experimentation by Strauer, Applicant's position remains that no undue experimentation would be required in order for one skilled in the art is validated. One skilled in the art having read Applicant's specification would readily understand that the placement of the entire array of stem cells harvested from bone marrow or blood in the body of a human patient would cause formation of an artery. Of course, such placement techniques are well known and documented in the art, leaving no need for more than routine experimentation. In this regard, see the comments contained in the complete article in The Journal of Invasive Cardiology, Vol. 17, July 1, 2005, entitled, "Progenitor Cell Transplantation and Function following Myocardial Infarction" (of record).

In the above-mentioned article, Dr. Pollman's spontaneous utterance that the TOPCARE study, "…uses a simple syringe injection system loaded with…bone marrow..." [Emphasis added]. Applicant believes that such quotation supports its position that no more than routine experimentation would be required to administer the materials of the claimed invention. Dr. Pollman's opinion is confirmed by the spontaneous utterance of Dr. Richard Heuser, a Declarant

of record, that "[t]he first time I saw this technique presented by the group [TOPCARE] in Frankfort, I was astonished at how simple it actually was…"

Strauer—just like Applicant—does not disclose that stem cell population is critical and does not describe any experimental protocol for selecting and isolating certain cells from the entire cell population described for the treatment therapy. Strauer does not describe using any experimental protocol to determine appropriate cell population, i.e., there is no requirement for using a specific subset of bone marrow stem cells.

Regarding time of treatment, Strauer does not disclose that determining time of treatment required experimentation. It is clear from the record that the treatment of myocardial infarction (MI) in human patients exhibiting either acute or chronic disease is considered. Strauer elected to treat patients from five to nine days after suffering an MI. Note that in a later publication, Strauer 2005 discloses treating chronic MI in patients that had transmural MI some 27 months earlier. Again, no experimentation regarding treatment time was noted. It is evident that the time of treatment following an MI is not a critical variable and undue experimentation would not be required. To the extent that the PTO may be relying on Strauer to establish that the time of administration is critical, Applicant points out that Strauer 2005 is the "best evidence" in regard to whether time of treatment in human patients is critical. Strauer 2005 teaches that stem cells can be used to successfully treat MI in human patients suffering either acute or chronic disease. The Examiner has alleged that Strauer 2005 indicated that *"as experimentation continues"* at page 10 of the Office Action. Such allegation is incredible when it is considered that Strauer indicated no experimentation and that timing was not indicated to be a significant factor by either Strauer or Strauer 2005. All that Strauer 2005 indicated is that the technique of Dr. Elia is successful at various times following damage to the heart. Moreover, Isner also does not

indicate that time is critical in the treatment of humans exhibiting ischemic heart tissue and this was not viewed as an impediment by the PTO. Thus, the PTO's conclusion that would be required to practice the claimed invention is not supported on the record and is fatally flawed.

At pages 42-45, ¶¶63-65 of the Office Action, the PTO addresses the two internet articles published in The Journal of Invasive Cardiology (of record). The Examiner acknowledged that the furnished copies of these publications were incomplete and attributed such lack of completeness to an error in converting web pages to .pdf format. It certainly was a remarkable coincidence that such error led to a one-sided analysis of the content of the publications. Notwithstanding such stated error, it is apparent from ¶64 of the Office Action that the present PTO Examiner read and relied upon the complete articles prior to the botched conversion. Accordingly, the comments provided by the present PTO Examiner in the 02/26/09 Office Action did not present an even-handed assessment of the respective articles because only portions allegedly favoring the Examiner's position were quoted and discussed. Such one-sided analysis does not accurately depict the content and context of the publications and is not considered to be appropriate for an *ex parte* proceeding. This biased analysis leads to an inaccurate assessment of the weight to be given to this evidence in evaluating enablement.

In any event, Applicant has again reviewed the limited context from the excerpts presented by the PTO but disagrees that the verbiage thereof rises to the level of evidence supporting non-enablement. Most of the comments concerned the BOOST, TOPCARE and Bio Heart trials. The latter body of work is dissimilar from the present invention in that it used a skeletal muscle myoblast product. Dr. Pollman from Guidant Corp. described the BOOST method, "as a simple syringe injection system loaded with 10 cc of bone marrow, 3 cc of which is applied to the coronary arteries." Dr. Pollman does not indicate that any further manipulation

was necessary. Applicant has consistently taken the position that the Strauer publication relied upon by the PTO describes little if any experimentation required to practice the disclosed implantation of bone marrow stem cells. Applicant makes the following comments regarding the excerpts presented by the PTO. Although the following comments were set forth above, Applicant hereby repeats these comments as a courtesy to the reader.

- The first quoted statement of Dr. O'Neil is merely asking a question that had been previously answered by Strauer.
- As Dr. O'Neil's second quoted question, neither Andreas Zelber (Guidant, Frankfort) nor Strauer reported any problem with cell hypoxia.
- Dr. ONeil's third question virtually confirms Applicant's argument that the specification teaches using unfiltered bone marrow.
- Dr. Nikol's comments sound like professional envy rather than critical analysis of bone marrow implantation.
- Dr. Gonschior's comments merely affirm that intravenous infusion would be the simplest method while Strauer's endocardial delivery may be the most efficient. These comments mirror the views expressed by Strauer.
- The quoted comments by Dr. Holmes merely express his criticism of premature human trials and appears to be especially directed to systemic infusion of cells.
- Dr. Whitlow's quoted comments are purely theoretical and do not evince that his opinions are based on the performance of any experimental or clinical trials. The autopsy findings described in Dohmann show that Whitlow's theoretical premises are not well founded.

It is puzzling that the PTO can conclude from such selective utterances that "[t]here was a general agreement that more experimentation was needed." This is particularly telling when one understands that the later work of Dohmann and Kornowski closely parallel Strauer's work.

The PTO's attention is again directed to the following erroneously omitted statements in the publications. Dr. Nikol stated that, "cells are considered a blood product." Dr. O'Neil stated that, "...because these bone marrow cells are pluripotential..." Another statements are the spontaneous utterance of Dr. Heuser that "[t]he first time I saw this technique presented by the group [TOPCARE] in Frankfort, I was astonished at how simple it actually was," and Dr. Pollman's statement that, "a simple syringe injection system" was used for implantation. The above utterances indicate that the treatment is not complex as alleged by the PTO.

The answer to the PTO's irrelevant question, "Why didn't "[Dr. Heuser] enlighten his colleagues?" is straightforward. Being a patentee in his own right, Dr. Heuser fully comprehends his duty in regard to confidential information, even if the Examiner is dismissive of such duty. Dr. Pollman, an employee of Guidant, was aware of confidentiality obligations regarding privileged information, as were all of the others. See the comment of Dr. Pollman near the bottom of the first page of the "Progenitor Cell Transplantation and Function following Myocardial Infarction" article (complete copy). In addition, an opinion regarding enablement based upon the disclosure of a patent application is distinct from optimizing medical processes, developing improvements to a basic process, and continuing research involving such processes to more fully understand the underlying mechanisms involved in the basic process. The Examiner's query and analysis of enablement clearly misses this point.

At page 45-48, ¶¶66-68 of the Office Action, the PTO has again taken issue with the lack of working examples in the specification. Specifically, the PTO has taken the stance that the

prophetic examples contained in the instant specification are inadequate for establishing a constructive reduction to practice of the claimed invention because of uncertainty expressed in the prior art as to whether cells, such as stem cells, would result in the formation of arteries. It is axiomatic that actual working examples are not required if the invention is disclosed in a manner that one skilled in the art would be able to practice it. Section 2164.02 of the MPEP states that:

> Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be "working" or "prophetic." A working example is based on work actually performed. A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved.

The PTO apparently believes that the specification's use of prophetic examples embodying cells containing active growth and transition factors does not form a basis for the enablement rejection. It has been Applicant's understanding from the beginning that prophetic disclosures are permitted under the rules, statute and case law. However, the PTO concludes, without further explanation, that the lack of actual examples "contribute significantly" to the determination of lack of enablement. It is the burden of the PTO to specifically and precisely point out why the absence of specific examples is a contributing factor.

Applicant recognizes that the medical arts in general are complex. However, while the physiological reactions involved may be complex, the practice of the claimed invention is straightforward. The called-for cells, e.g., stem cells, the methods of administering, and the particular apparatus required for administering the cells, are old and well known in the medical arts.

The present PTO Examiner has acknowledged at page 23, ¶32 in the Office Action of September 28, 2008 in co-pending application Serial No. 09/794,456 that it "cannot, and does

not, demand human clinical trials to demonstrate enablement…". Applicant appreciates such pronouncement since the previous actions by the PTO lead Applicant to believe that the method and manner of making the claimed invention was the predominant contributing factor in the PTO's determination of lack of enablement. However, Applicant is not sure of the present PTO Examiner's understanding of the nature of clinical trials in view of the misunderstanding of the design of the previously discussed Strauer tests.

It appears that the PTO puts forth the proposition that there is a higher "enablement" standard required by the statute for "cases that involve unpredictable factors such as most chemical reactions and physiological activity" while citing case law presumably "codifying" such a higher standard. In other words, the PTO is placing a higher burden on Applicant to support enablement because of the nature of the claimed invention. The PTO is relying on case law because the first paragraph of Section 112 does not embody such a separate requirement for chemical and physiological related inventions *vis-à-vis* other classes of inventions. What is certain is that the question of enablement must be determined on a case-by-case basis taking into consideration the facts presented. The specification discloses all the information that is needed for one skilled in the art to: 1) select bone marrow stem cells harvested from the patient; and 2) intramuscularly injecting said stem cells into sites of ischemic tissue for promoting differentiation and morphogenesis into new blood vessels, i.e., arteries and cardiac muscle.

Applicant notes the PTO's gratuitous justification for the granting of the Isner and Kornowski patents. It is certainly not Applicant's position that these patents should not have been granted. Rather Applicant has pointed to certain facts contained in such patents that were not an obstacle to allowance. Applicant also notes that the PTO has attempts to distinguish between the prophetic examples of Applicant and the admittedly prophetic examples of

Kornowski on the basis that Kornowski had animal studies. Such purported distinction is meaningless when it is considered that prophetic examples are permitted under current law. Assuming, *arguendo*, that the PTO somehow met the burden of establishing a *prima facie* case of lack of enablement, Applicant believes that any such case has been rebutted by the weight of the evidence contained in the Declarations of experts in the field—Drs. Heuser and Lorincz. The conclusions set forth in the respective Declarations establish an objective fact that is highly material to a determination of enablement. Drs. Heuser and Lorincz, both highly skilled medical experts, read relevant portions of the specification, including generic as well as those drawn to elected and non-elected species, and reached the determination that one skilled in the medical arts, armed with the knowledge in the disclosures, would be enabled to practice the claimed method and to predictably anticipate the results defined therein without need for resorting to undue experimentation. See paragraphs 3-6 of the Fourth Supplemental Declaration of Dr. Richard Heuser and paragraphs 3-6 of the Third Supplemental Declaration of Dr. Andrew E. Lorincz.

The PTO, at pages 45 and 46, ¶63 of the Office Action contended that opinions of experts, Drs. Heuser and Lorincz, in regard to the ultimate legal conclusion of enablement are entitled to no weight, citing In re Lindell and In re Chilowsky for precedent. The above case law was cited as standing for the proposition that enablement is a question of law. However, it is clear from MPEP 2164.05 that declarations are evidence that must be considered and that weight must be accorded based on the factual evidence presented therein supporting a conclusion of enablement. The Court in In re Buchner, supra, held that "expert's opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement." In In re Buchner, supra the PTO determined that the specification lacked enablement because elements

necessary for carrying out the invention were neither disclosed therein nor well-known to those of ordinary skill in the art. The Court, while recognizing that the Buchner specification need not disclose what is well known in the art, agreed with the PTO that unless the identified missing elements were well-known in the art, the application must provide such information and that "it is not sufficient to provide it only through an expert's declaration." The present factual pattern is clearly distinct from that of Buchner in that the PTO has conceded in other related applications that the administration of cells was known in the medical art at the time of the present invention. It is further established in this record that the compositions (stem cells such as bone marrow stem cells), implantation apparatus (hypodermic needle) and treatment methods disclosed in the specification were well-known in the medical art. Contrary to the PTO's position, Applicant's evidence of enablement is supported by more than Declarants' conclusory statements. Declarants identify and rely upon facts, i.e., specific portions of the disclosure in the instant specification which support their conclusions that one skilled in the art would be able to make and use the claimed invention. Declarants' reading and understanding of the identified portions of the specification mentioned in Paragraph 5 of the Fourth Supplemental Declaration of Dr. Heuser and in the Third Supplemental Declaration of Dr. Lorincz, compels a conclusion that Dr. Elia was in possession the concept of implanting bone marrow stem cells and growing arteries and cardiac muscle in the heart of a human patient.

The PTO dismissed Applicant's declaration evidence as merely managing "to piece the general idea of the instant claims together" by combining juxtaposed portions of the specification, not the complete specification. This is yet another instance of the procedural error in the handling of the prosecution of the instant application. By failing to articulate adequate reasons to rebut the Declarations of Drs. Heuser and Lorincz, the PTO "failed to consider the

totality of the record for the purpose of issuing a final rejection and thus erred as a matter of law." In re Alton, 76 F.3d 1168, 37 USPQ2d 1578 (Fed.Cir. 1996). It is trite law that the PTO must consider the probative value of such evidence *vis-à-vis* any asserted *prima facie* case. See In re Oetiker, at 1445, 24 USPQ 2d at 1444. In re Keller, 642 F.2d 413, 208 USPQ 871, (CCPA 1981). In the absence of critical analysis, the PTO appears to be relying solely upon its opinion rather than assessing weight to the objective evidence proffered in the Declarations. PTO Examiners, not being skilled persons in the medical art, must give weight to these expert opinions rather than substitute the opinion of the PTO. See In re Neave, 370 F.2d 961, 152 USPQ 274, (CCPA 1967).

Moreover, the PTO stated that:

> The thread that connects the pieces of the generic concept also runs through hints of non-existent methods, unidentifiable cells, nonsensical method steps, and most importantly, predictions of results that are either incredible or directly contradicted by subsequent disclosures.

Such statement constitutes further evidence of the improper prosecutorial handling of the instant application. The above quotation evinces a pattern of attempted deflection from the absence in the record of objective evidence on the part of the PTO required for establishing a *prima facie* case of nonenablement. The present PTO Examiner's conclusion that, "The choice of cell to be administered to achieve the recited outcome was not known in the prior art …." is further evidence of a continued failure to review the subject specification with an open knowing mind. Of course, the obtention and therapeutic use of human bone marrow cells *per se* has been known in the medical arts for decades. The specification clearly describes obtaining bone marrow cells and using such cellular compositions for promoting differentiation and morphogenesis (growth) of soft tissues. It is self evident that applicant's claimed use of such

cellular composition for growing arteries was not known at the time of filing, otherwise, the claimed invention would be subject to a rejection for lack of novelty.

Finally, the PTO states that the sections of the specification cited in the declarations have been thoroughly considered. However, no analysis or rebuttal to the expert opinions has been presented. Rather the mere opinion of the present PTO Examiner, a non-expert in the medical art appears. This is error because the declarations provide evidence that rebuts any *prima facie* case of obviousness established by the PTO. In this regard, the PTO is further referred to the materials from Applicant's Appeal Brief set forth above.

At ¶70 of the Office Action, the PTO correctly points out that Wands presented working examples whereas the present application is based on a prophetic disclosure. Applicant is aware of such distinction and has never asserted otherwise. The PTO further correctly states that the prophetic examples disclosed in Applicant's specification "lack support by experimental evidence." However, the PTO' contention that the claimed potential of bone marrow cells, i.e., for tissue regeneration, is either incredible or directly contradicted by evidence in the record is a nonsensical notion that lacks professional credibility. Applicant's declaration evidence, Strauer, and Strauer 2005 support the predictability of the claimed invention. In addition, the PTO has issued the Kornowski patent attesting to the predictability of the regenerative potential of bone-marrow stem cells in the treatment of chronic heart disease. It is clearly evident that the PTO did not question the predictability of the result achieved by Kornowski. Puffery and hubris aside, it is clear to Applicant that the main impediment in his quest for patent recognition rests in the prophetic manner in making this pioneer discovery.

In any event, The PTO's attention is once again directed to the In re Wands decision, which led to the grant of a patent. The Court found that the PTO's determination of

nonenablement was unsupported by the evidence in the record. The Court further noted that the skill level in the art was high and that known materials were utilized in the practice of the invention in weighing the evidence. The instant fact situation is similar to that of In re Wands because the skill level is also high and known administration techniques and known materials are also utilized in the practice of the invention. In addition to such factual parallelism, Applicant provided expert objective evidence in the form of the Declarations of Drs. Heuser and Lorincz. These medical experts read relevant portions of the specification setting forth the generic invention and elected and non-elected species of such generic invention and determined that one skilled in the medical art, armed with the guidance and direction in the specification disclosures, would be enabled to practice the methods defined in the claims on appeal and to predictably anticipate the results defined therein without need for resorting to undue experimentation. Regarding complexity, the PTO is again referred to the spontaneous utterances mentioned above wherein the process was characterized as being simple by doctors skilled in the art. When the guidance and direction provided by Applicant's specification disclosure, the level of knowledge and the content of the prior at the time of the invention as established in the record, the high level of skill in the art, and Applicant's declaration evidence are interpreted in a reasonable manner, analysis considering the factors in In re Wands compels a conclusion that undue experimentation would not be required to practice the invention called for in the appealed claims.

The PTO's citation and reliance on the Genentech at page 71 of the Office Action is inapt. Applicant has consistently pointed out wherein the specification provides guidance for carrying out the claimed invention. The PTO seems to be under the impression that all that is

required to support an enablement rejection is to repeat by rote case law without significant analysis establishing precedent *vis a vis* the evidence in chief relied on for a *prima facie* case.

Once the relevant materials and administration techniques set forth in Applicant's specification and those known in the art when the application was filed, are properly considered in their entirety, Applicant believes that there should be no question that one skilled in the medical art is enabled to make and use the claimed invention. This conclusion is reinforced by the fact that the materials and administration techniques, but not the inventive result, were well known when the instant application was filed.

New Provisional Rejection–Nonstatutory
Obviousness-Type Double Patenting

It is noted that the PTO withdrew all prior double patenting rejections and introduced a new provisional nonstatutory obviousness-type double patenting rejection.

The new ground of nonstatutory obviousness-type double patenting indicated that claims 403 and 407-412 were provisionally rejected as being unpatentable over claims 161-164 and 172-174 of co-pending application Serial No. 10/179,589. The PTO's statement at page 53, ¶74 of the Office Action that, "Therefore, Applicant indicates that step (b) inherently occurs every time step (a) is performed" is not correct. Such statement is only correct when a bud is formed. In any event, Applicant stands ready to submit an appropriate Terminal Disclaimer upon an indication of allowable subject matter related to such claims.

For reasons set forth above, Applicant believes that the instant application is in condition for allowance and a notice to such effect is requested.

Respectfully submitted,

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